Aventis, GCP QA
Audit Report - Study No. : HMR3647A/ 3014
Investigator: Anne Kirkman-Campbell, MD
423 South Third Street
Gadsden, AL 35901

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Audit Date: January 17-18, 2002

CLINICAL STUDY - AUDIT REPORT

Preliminary ☒ Final ☐ Date of Report February 5, 2002

Internal Audit Date On-Site Audit Date Jan. 17-18, 2002

Study No. HMR3647A/ 3014 Investigator No. 1129
Investigator:
Anne Kirkman-Campbell, MD
423 South Third Street
Gadsden, AL 35901
Audit Site (if different)

Other facilities seen: None.

Study Manager : Nadine Grethe, Aventis Pharmaceuticals, Bridgewater, USA

Site Monitor(s) : Christianne Hammond, Sr. CRA, PPD Development, Jerry Ferguson, CRA, PPD Development, Abigail Wear, Site Management CRA, PPD Development

CRO: PPD Development, Quintiles and Dimensional Health Care (DHC)

Status of the Study ☐ Planned ☒ Ongoing ☐ Completed
Enrollment date of first patient October 19, 2001

Number of Subjects Planned: 4 to 50 Enrolled: 327 Completed: 177

Subject Numbers Audited Full : 060, 080, 100, 140, 180, 191, 200, 220, 240, 280 Partial:

Participants in the Audit	Name	Function
Site Staff	Anne Kirkman-Campbell, MD	Investigator
	Michelle Snedeker	Study Coordinator
Aventis Staff	Ranjan Khosla, MBBS, MD, CQA	Auditor
CRO Staff		

Responsible Auditor: Ranjan Khosla, MBBS, MD, CQA, Aventis Bridgewater

Report Signature/Date Ranjan Khosla February 5, 2002
5/11/2002

SUMMARY

Purpose of Audit

The purpose of the audit was to assess compliance with the protocol and appropriate GCP requirements and applicable Global SOPs.

For United States: The standards used in the performance of this audit were the U.S. code of federal regulations and guidelines as set out in 21CFR parts 11, 50, 54, 56 and 312.

Selection of Investigator

Routine ☒ For cause ☐

If for cause, please specify:

Overview

The Study Coordinator entering the date for the PI and/or the subjects on the ICFs; the PI entering the date for the person obtaining the consent and/or the subjects; partial compliance to the CFR 312.62 requirement that the case history of each individual shall document that informed consent was obtained prior to participation in the study; and other problems pertaining to informed consent are significant issues that require corrective action.

Recommended Corrective Action

No action indicated	☐
Immediate action required	☐
Corrective action during routine monitoring	☒

AUDIT FINDINGS

Below are details of significant findings. Additional audit findings are listed in Attachment I. Audit finding category & sub-category checklist is Attachment II.

FINDING #	CATEGORY #	SUB-CATEGORY #
1	3	3.2
FINDING: The review of the medical charts for all the subjects showed no dated entry in the source documents at the time of screening/enrollment that the subjects signed the Informed Consent Form [ICF] and a copy of the ICF was given to the subjects. Instead, the site inserted a photocopy of a document that stated: 1. Subject signed consent and was given a signed and dated copy of ICF. 2. Subject met entry criteria. 3. Subject was enrolled in the TREAT study protocol # HMR 3647A/ 30. 4. LFT- visit 1 and visit 2. This document did not have the subject identifiers or the date. When questioned, the PI confirmed that this document was placed in each subject's medical charts at a later date when the site became aware of this requirement by newsletters sent out by PPD.		
DISCUSSION/COMMENT: CFR 312.62 requires that the case history of each individual shall document that informed consent was obtained prior to participation in the study.		
RECOMMENDATION Please submit a Memo to File or record as a late entry in the medical charts that the subjects signed the ICF and were given a copy of the consent form prior to their participation in the study.		

CORRECTIVE ACTION:	Not resolved	Implemented	Agreed to be Implemented
	☒	☐	☐

FINDING #	CATEGORY #	SUB-CATEGORY #
2	3	3.2
FINDING: The ICF has a place for the subject to sign and date, for the person obtaining consent to sign and date and for the Principal Investigator [PI] to sign and date. In the ICFs for the following subjects, the Study Coordinator has entered the date for the subjects: 016, 027, 029, 033, 042, 046, 049, 050, 052, 056, 057, 061, 164, 167, 184, 207, 210, 217, 221, 222, 224, 234, 248, 249, 268, 276, 281, 282, 283, 290, and 301. In the ICFs for subject: 014, the PI has entered the date for the subject. In the ICFs for the following subjects, the PI has entered the date for the Study Coordinator who had obtained the consent: 001, 002, 003, 004, 005, 006, 007, 026, and 194.		
DISCUSSION/COMMENT: 21 CRF 50.27 and ICH 4.8.8 require that prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.		
RECOMMENDATION Please request the site to document in a Memo to File that the ICFs were dated by the PI/ Study Coordinator and send a copy of this Memo to the IRB and to PPD.		

CORRECTIVE ACTION:	Not resolved	Implemented	Agreed to be Implemented
	☒	☐	☐

FINDING #	CATEGORY #	SUB-CATEGORY #
3	3	3.2

FINDING: The ICF has a place for the person obtaining consent to sign and date and for the Principal Investigator [PI] to sign and date. In the ICFs for the following subjects, the Study Coordinator has entered the date for the PI which makes it difficult to elucidate exactly on which date the PI signed the ICF: 008, 009, 010, 011, 012, 013, 014, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 025, 027, 028, 029, 030, 031, 032, 033, 034, 035, 036, 037, 036, 037, 038, 039, 040, 041, 042, 043, 044, 045, 046, 047, 048, 049, 050, 051, 052, 053, 054, 055, 056, 057, 058, 059, 060, 061, 062, 063, 064, 066, 067, 068, 070, 085, 086, 088, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 177, 179, 180, 181, 182, 183, 184, 185, 187, 188, 189, 190, 191, 192, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, and 327.

DISCUSSION/COMMENT: Since the IRB approved the ICF with a required field of the PI's signature and date, the intent is to document that the PI is aware that the subject has entered the study and that the PI reviews the study related documents at regular intervals. When the Study Coordinator enters the date for the PI it makes it difficult to elucidate exactly on which date the PI signed the ICF.

RECOMMENDATION
Please request the site to document this issue in a Memo and send a copy of this Memo to the IRB and to PPD.

CORRECTIVE ACTION:	Not resolved	Implemented	Agreed to be implemented
	☒	☐	☐

FINDING #	CATEGORY #	SUB-CATEGORY #
4	14	14.1

Finding: The site personnel were performing pregnancy tests to determine eligibility for the study. To date, the site has not obtained a CLIA Certificate of Waiver.

DISCUSSION/COMMENT: 42 CFR Part 493.5 requires that when the site personnel perform pregnancy tests to determine eligibility for the study then the site needs to obtain a CLIA Certificate of Waiver.

RECOMMENDATION :
Please document in a Memo to File that site personnel performed pregnancy tests to determine eligibility for the study without obtaining a CLIA Certificate of Waiver. Please obtain a CLIA Certificate of Waiver.

CORRECTIVE ACTION:	Not resolved	Implemented	Agreed to be implemented
	☒	☐	☐

FINDING #	CATEGORY #	SUB-CATEGORY #
5	5	5.1, 5.2

Finding: During the exite interview, it was confirmed that the PI and the Study Coordinator are not aware of the complete definition and reporting requirements of Adverse Events of Special Interest [AESI] and the Serious Adverse Events [SAEs].

DISCUSSION/COMMENT: Section 8.1.4 of the protocol specifies that AESIs include:

- Hepatic: reports of hepatitis, jaundice, worsening of a pre-existing hepatic condition, or ALT ≥3 x upper limit of the normal range.
- Cardiac: torsades de pointes, ventricular arrhythmias, syncope as defined by total loss of consciousness, cardiac arrest, or unwitnessed or unexplained death.
- Vasculitis: purpura or other signs of vasculitis.
- Visual: blurred vision.

RECOMMENDATION :
Please retrain the site about the AESIs and SAEs and their reporting requirements. Please document this training.

CORRECTIVE ACTION:	Not resolved	Implemented	Agreed to be Implemented
	☒	☐	☐

FINDING #	CATEGORY #	SUB-CATEGORY #
6	14	14.1

Finding: The PI has enrolled as subjects in the study, the Study Coordinator and her staff members Autumn Gajda and Amanda Dunn who are listed on the "TREAT Study Personnel Signature/ Responsibility Log".

DISCUSSION/COMMENT: It is the opinion of GCP QA at Aventis that it is not a good practice for the Principal Investigators to enroll themselves or their staff members or close relatives. There are no particular objections to this type of enrollment as per GCP guidelines (at least this is not properly covered "in the text"), if all the rules regarding the patient free consent after receiving adequate information about the study are complied with. However, we recommend avoiding this type of recruitment as it is always difficult to demonstrate that this was managed properly and that no conflicts of interest occurred due to the particular relationship Investigator - Staff Member. There is also the issue with data confidentiality and access to those data by other staff members, including Sponsor's representatives during monitoring, etc.

RECOMMENDATION :
Please request the PI not to enroll her staff members or close relatives in this and future Aventis studies.

CORRECTIVE ACTION:	Not resolved	Implemented	Agreed to be Implemented
	☒	☐	☐

ATTACHMENT I.

ADDITIONAL FINDINGS

Below is a listing of minor non-compliance observations. Some of these findings require individual responses and are so designated. For the other findings listed, an item by item response is unnecessary. One response indicating corrective actions for all these items would be sufficient. Alternatively, the response for several findings may be grouped.

Find-ing #	Categories Main.Sub	Subject's number, if applicable	Individual Response Required	Finding
1	1.1		YES	In section 7 of the FDA Form 1572 the number of the protocol is HMR 3647A/ 3014 A. In the protocol version date September 27, 2001 the protocol number is HMR 3647A/ 3014. Please clarify and document in a Memo to File.
2	2.1		YES	The 2002 Membership Roster of the Copernicus Group Independent Review Board was not present at the site. Please obtain and file the 2002 Membership Roster.
3	3.2	006	YES	The ICF has a place for the person obtaining consent to sign and date and for the Principal Investigator to sign and date. In the ICFs for subject 006, the PI did not write the year in the date section. Please request the PI to complete the date section of the ICF in current date.
4	3.2	082, 083, 085, 089, 137, 181, 307, 308, 309, 310, 311	YES	The ICF has a place for the subject to sign and date, for the person obtaining consent to sign and date and for the Principal Investigator to sign and date. In the ICFs for subjects 082, 083, 085, 089, 137, 181, 307, 308, 309, 310 and 311 the subject has signed the ICF 1-2 days earlier than the PI and the person obtaining consent. Please request the site to document in a Memo to File and submit a copy of the Memo to the IRB and to PPD. Please retrain the site that the person obtaining consent must sign and date on the day the consent is obtained.
5	3.2	237, 239, 242	YES	The ICF has a place for the subject to sign and date, for the person obtaining consent to sign and date and for the Principal Investigator to sign and date. The subjects signed the ICF on 12/28/01 and the PI and Study Coordinator signed the ICF on 1/7/02. Please request the site to document in a Memo to File and submit a copy of the Memo to the IRB and to PPD. Please retrain the site that the person obtaining consent must sign and date on the day the consent is obtained.

6	3.2	289	YES	The ICF has a place for the subject to sign and date, for the person obtaining consent to sign and date and for the Principal Investigator to sign and date. The subject signed the ICF on 1/10/02 and the PI and Study Coordinator signed the ICF on 1/14/02. Please request the site to document in a Memo to File and submit a copy of the Memo to the IRB and to PPD. Please retrain the site that the person obtaining consent must sign and date on the day the consent is obtained.
7	3.2	054	YES	The ICF has a place for the subject to initial each page of the ICF. The initials of the subject on page 1 do not match the initials on page 2-5. Please request the site to clarify and document.
8	3.2	159, 162, 235, 236	YES	The ICF has a place for the subject to initial each page of the ICF. The subject has not initialled all the pages of the ICF. Please request the site to have the subject initial these ICF pages in the current date.
9	3.2	275	YES	The Study Coordinator had obtained the consent but had not signed the ICF. Please request the Study Coordinator to sign the ICF in current date and document in a Memo to File.
10	3.2	088, 110, 204, 292	YES	The PI has not signed the ICF. Please request the PI to sign the ICF in current date.
11	3.2	087, 257, 262, 266	YES	The subject signature date has overwrites. The actual date is not clear. Please request the site to clarify.

12	3.2	174	YES	The subject dated the ICF 11/17/01 instead of 12/17/01. Please request the site to clarify and document.
13	3.2	324	YES	The subject dated the ICF 1/15/01 instead of 1/15/02. Please request the site to clarify and document.
14	3.2	090, 099, 232	YES	For subject 090, the page number 4 of the ICF is not present at the site. For subjects 099, and 232 page 3 of ICF is not present. Please request the site to obtain a copy from the duplicate given to the subjects.
15	4.6	080, 191	YES	Visits 2 and 3 are out of the window prescribed by the protocol. Please request the site to document this protocol violation in a Memo to File and inform the IRB and PPD.
16	4.6	100, 180, 200	YES	Visits 3 is out of the window prescribed by the protocol. Please request the site to document this protocol violation in a Memo to File and inform the IRB and PPD.
17	4.6	140	YES	Visit 2 is out of the window prescribed by the protocol. Please request the site to document this protocol violation in a Memo to File and inform the IRB and PPD.
18	6.5		YES	There are several overwrites/ corrections without initials and date on the Drug Accountability Log. Please retrain the site about the GCP compliant corretion procedures.

19	6.3		YES	The Study Coordinator informed the Auditor that she had to open each carton of Augmentin® to get the lot number of each bottle. The sites are required to record each drug shipment in the first three columns when received, indicating date, lot number (for Augmentin®) or part number (for Ketek®), and drug name in the Drug Accountability Log. The Augmentin bottles have the lot number and the Augmentin carton has the part number. Therefore the site must open the carton to obtain the lot number and write this on the drug log. This issue is not unique to this site and had been discussed with Nadine Grethe, SM and it was decided that the Drug Accountability Log will be modified to record the part number for Augmentin® and part number for Ketek® at the time of the receipt of the drug by the site. When the site randomizes a subject, then the lot number can be obtained from the Augmentin® bottle for recording on the Drug Accountability Log.
20	8.2	060	YES	For subject 060, the diagnosis of Acute Exacerbation of Chronic Bronchitis noted on the CRF page 1 for visit 1 is not recorded on the Source Documents dated 11/27/01. Please request the site to clarify and document.
21	8.2	180	YES	For subject 180, "Coronary Artery Disease" and "Other Cardiovascular Disease" are not noted on the CRF page 1 of Medical History, but on the progress notes dated 7/12/01, Coronary Artery Disease and Hypertension are noted. Please request the site to document Medical History on CRF page 1.
22	11.2		YES	CV is not present for Michele Snedeker [Study Coordinator], Autumn Gajda and Amanda Dunn who are listed on the "TREAT Study Personnel Signature/ Responsibility Log". Please add a copy of their CV to the study file.
23	13.1		YES	The updated copy of the following documents was not present in the files of Investigator (ISF): The PI's License to Practice Medicine in Alabama expired on 12/31/01. The PI's Controlled Substances Registration Certificate expired on 12/31/01. Please request the site to update the ISF.
24	13.1		YES	All pages of the "TREAT Phone Log" are blank. Please request the site to complete the "TREAT Phone Log" regularly.
25	13.1		YES	The subject identification code list and the subject enrollment log are incomplete. Please request the site to complete the subject identification code list and the subject enrollment log.

26	14.1	226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239	YES	The white, yellow and pink pages of the CRF do not match each other. Please request the site to retain photocopies of the white CRF page with the discrepant yellow and pink pages and document this CRF printing error.
27	14.1		YES	The follow up letter of the the Interim Monitoring Visit performed on 11/29/01 was not present at the site. Please provide a copy of the follow up letter to the site.

ATTACHMENT II.
AUDIT FINDING CATEGORIES

		COMPLIANCE		NON-COMPLIANCE	
	Not done	OK	Minor	Significant
1. Regulatory requirements				
1.1 Submission to regulatory authorities/agencies	☐	☐	☒	☐
1.2 Approval by regulatory authorities/agencies	☐	☒	☐	☐
1.3 Continuing information to regulatory authorities/agencies	☐	☒	☐	☐
1.4 Other required (local) regulatory documents	☐	☒	☐	☐
1.5 Financial/insurance and/or legal documents/requirements	☐	☒	☐	☐
2. Ethics Committee IEC/IRB requirements				
2.1 Membership (list) of IRB/IEC	☐	☐	☒	☐
2.2 Submission to IRB/IEC	☐	☒	☐	☐
2.3 Approval by IRB/IEC	☐	☒	☐	☐
2.4 Continuing information to IRB/IEC	☐	☒	☐	☐
3. Informed Consent				
3.1 Content of informed consent document (including subject information)	☐	☒	☐	☐
3.2 Obtaining informed consent and/or documentation thereof	☐	☐	☐	☒
4. Study conduct/protocol adherence				
4.1 Adherence to inclusion/exclusion criteria	☐	☒	☐	☐
4.2 Adherence to randomisation procedure (e.g. not followed/blind not maintained)	☐	☒	☐	☐
4.3 Administration of investigational products (including deviations in compliance check)	☐	☒	☐	☐
4.4 Conduct of study related procedures/visits (e.g. not per protocol)	☐	☒	☐	☐
4.5 Prohibited concomitant treatment or medical condition during trial	☐	☒	☐	☐
4.6 Other non-adherence to protocol	☐	☐	☒	☐

	Not done	OK	Minor	Significant
5. Safety, AEs and SAEs				
5.1 AEs by investigator to sponsor/CRO	☐	☐	☐	☒
5.2 SAEs by investigator to sponsor/CRO	☐	☐	☐	☒
5.3 SAEs internally within sponsor/CRO	☐	☒	☐	☐
5.4 SAEs by sponsor/CRO to investigator	☐	☒	☐	☐
6. Investigational products				
6.1 Sending/delivery and receipt	☐	☒	☐	☐
6.2 Storage/handling	☐	☒	☐	☐
6.3 Labelling	☐	☐	☒	☐
6.4 Returning	☒	☐	☐	☐
6.5 Accountability	☐	☐	☒	☐
6.6 Destruction	☒	☐	☐	☐
7. Source documents				
7.1 Availability and completeness of source documents and source data	☐	☒	☐	☐
7.2 Accuracy of source documents and source data	☐	☒	☐	☐
7.3 Documentation supporting computerised source documents and source data	☒	☐	☐	☐
7.4 Direct access to original source documents (direct SDV)	☐	☒	☐	☐
8. Handling of reported data				
8.1 Content and structure of CRFs in comparison with study protocol	☐	☒	☐	☐
8.2 Completeness/availability of data in CRF, including source data not transferred to CRF	☐	☐	☒	☐
8.3 Accuracy-discrepancies between data recorded in CRF and source documents	☐	☒	☐	☐
8.4 Procedure of correction	☐	☒	☐	☐
8.5 Data transmission to sponsor/CRO	☒	☐	☐	☐

	Not done	OK	Minor	Significant
9. Equipment and facilities				
9.1 Equipment concerning presence, function, and use	☒	☐	☐	☐
9.2 Equipment concerning maintenance, calibration and validation (including computer systems)	☒	☐	☐	☐
9.3 Archiving facilities for study related documents and for subjects' (medical) records	☐	☒	☐	☐
9.4 Facilities to perform study related procedures/processes (e.g. CXR, MRI, EKG)	☒	☐	☐	☐
9.5 Handling of biological specimens on-site (sampling, handling, labelling, storage, etc.)	☐	☒	☐	☐
10. Clinical laboratory (central or local)				
10.1 Transport of biological specimens	☒	☐	☐	☐
10.2 Documentation, certification, validation, etc.	☐	☒	☐	☐
10.3 Procedures (e.g. handling of samples)	☐	☒	☐	☐
10.4 List(s) of normal ranges and units	☐	☒	☐	☐
11. Organization and responsibilities on-site				
11.1 Delegation by investigator	☐	☒	☐	☐
11.2 CVs of key personnel	☐	☐	☒	☐
11.3 Training and/or documentation of (key) personnel	☐	☒	☐	☐
11.4 Supervision of study staff	☐	☒	☐	☐
11.5 Investigator involvement	☐	☒	☐	☐
12. SOP compliance/problems				
12.1 Complying with applicable HMR monitoring (global and local) SOPs	☐	☒	☐	☐
12.2 Complying with all other applicable HMR (global and local) SOPs	☐	☒	☐	☐
13. Essential documents				
13.1 Presence, completeness and adequacy of documents in files of investigator/institution (ISF)	☐	☐	☒	☐
13.2 Presence, completeness and adequacy of documents in files of sponsor/CRO (TMF)	☒	☐	☐	☐
14. Miscellaneous			☐	☒
14.1 Items reviewed but not classified in other categories/subcategories			☐	☒

ATTACHMENT III.

CONFIRMATION OF RECEIPT AND FOLLOW-UP (Study Manager)

Please confirm receipt of this preliminary audit report by signing this page.

Please review the findings and suggested recommendations provided in this report. The corrective action plan should include a description of the activity(ies) that will be undertaken to correct the non-compliance and indicate by whom and when they will be conducted. Responses to this report may be given either by commenting directly on the report pages or by including a follow-up sheet. The significant findings presented in the Audit Findings section of this report as well as the findings requiring an individual response in Attachment I, must be responded to individually. The additional findings listed in the Attachment I should also be addressed. However, one response may be sufficient to cover several of these findings.

Comments from the monitor (and other persons involved) should be addressed within your response.

Please return the preliminary audit report and your comments within 20 working days to the responsible auditor. The responsible auditor will review the comments and corrective action and respond if any additional action is required. Thank you very much in advance.

Study Manager

Place Aventis Date 22/04/2002 (dd/mm/yyyy)

Name Nadine Briethe

Signature N-L

Feedback/Follow-up

Please check as appropriate:

- ☐ No comments/corrective action necessary
- ☐ Comments/corrective actions made in the text of the audit report directly
- ☒ Comments/corrective actions given on a separate sheet of paper.

ATTACHMENT IV.

CONFIRMATION OF RECEIPT (Site Monitor/Other)

Please confirm receipt of this preliminary audit report by signing this page.

This copy of the audit report is for your information. The responsibility for coordinating the final response is with the Study Manager.

Please return this copy within 20 working days to the responsible auditor. Thank you very much in advance.

Site Monitor/Other

Place PPD Development, Inc. Date 19/Apr/2002 (dd/mm/yyyy)

Name Pamela Bullock, Sr. CRA

Signature Pamela Bullock